Citation:

Huncharek M, Muscat J, Kupelnick B. Impact of dairy products and dietary calcium on bone-mineral content in children: Results of a meta-analysis. *Bone*. 2008; 43 (2): 312-321

PubMed ID: 18539555

Study Design:

Meta-analysis or Systematic Review

Class:

M - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To determine the relationship between dietary calcium and dairy derived nutrients on bone mineral content (BMC) in children by statistical pooling of available published data.

Inclusion Criteria:

- Eligibility criteria for the studies were determined prospectively, as were the specific data points to be extracted from each included report
- A plan for data analysis was also formulated as part of the study protocol
- A data extraction form was designed for recording relevant data from each published report
- Data extraction was performed by two researchers with differences in extraction forms resolved by consensus.

Criteria for Literature Search

- An English language search covering the years 1966 through 2006 was performed using MEDLINE, Current Contents (up to March 2003) and the Cochrane Database. Terms used were bone/bones, dairy products, calcium and calcium/dietary
- The electronic database searches were supplemented by manual searching of bibliographies of all retrieved papers as well as textbooks and relevant review articles. If a series of papers was published, all data were retrieved from the most recent report. A relevant database was also reviewed and served as an addition source of references for the meta-analysis
- The initial citations (in the form of abstracts) were screened by a physician investigator to exclude those that did not meet protocol inclusion criteria
- Full papers of the remaining citations were subsequently screened for eligibility using the following criteria:
    - Studies enrolling patients 18 years old and younger
    - Must be a randomized controlled trial (RCT) or observational study design
    - Must contain information on the outcome of interest [i.e., bone mineral content (BMC)]

- RCTs must have a sample size of at least 50 subjects
- Specified selection criteria for intervention and control subjects and randomization procedures.

Citations meeting the above criteria were entered into an accept log.

Exclusion Criteria:

- Animal studies, *in vitro* studies, letters to the editor, review articles, abstracts, non-peer reviewed work, studies of children with chronic diseases that could confound the analysis including gastrointestinal disease capable of inducing malabsorption, congenital or acquired bone disease and presence of fracture
- Rejected citations were also tabulated and entered onto a reject list with the reasons for rejection specified.

Description of Study Protocol:

Recruitment

Not applicable.

Design

Meta-analysis.

Dietary Intake/Dietary Assessment Methodology

Not applicable.

Blinding Used

Not applicable.

Intervention

Not applicable.

Statistical Analysis

Randomized trial data were analyzed by statistical procedures that were a modification of the Mantel–Haenszel method and was based upon a fixed effects model.

- If data were presented as measures on a continuous scale, the methods described by Cochrane were employed. This method is an extension of analysis of variance where the "groups" are studies. Initially the mean difference in outcome measure between groups was estimated followed by calculation of the pooled variance for each study and calculation of a weight. A summary mean was then calculated. If studies reported absolute change from baseline measurements and endpoint data were not available, absolute values were calculated using the standard deviation of the baseline data for the endpoint standard deviation (SD)
- Along with estimation of a summary estimate of effect, a statistical test for homogeneity was performed (Q). This procedure tests the hypothesis that the effect sizes are equal in all of the

studies analyzed. If Q exceeds the upper tail critical value of Chi-square ($P<0.05$) at k-1 degrees of freedom (where *k* equals the number of studies analyzed or number of comparisons made), the observed variance in study effect sizes is significantly greater than what would be expected by chance if all studies shared a common population effect size. If the hypothesis that the studies are homogenous is rejected, the studies are not measuring an effect of the same size. In this instance, calculation of a pooled estimate of effect may be of questionable validity. Possible explanations for the observed heterogeneity must then be sought to provide the most rational interpretation of the summary estimate of effect. Therefore, they performed sensitivity or further stratified analyses as needed based on the magnitude of Q; these analyses are discussed below

- The potential for publication bias was not statistically examined. Publication bias may occur because published studies are not representative of all studies ever done. The funnel plot method and other techniques have been developed in an attempt to address this issue. Unfortunately, these methods lack firm statistical theoretical support and are not generally recommended for medical applications.

Data Collection Summary:

Timing of Measurements

Not applicable.

Dependent Variables

Total body bone mineral content was measured using dual energy X-ray absorptiometry (DEXA) in all but one of the studies included in the meta-analysis.

Independent Variables

Not applicable.

Control Variables

Not applicable.

Description of Actual Data Sample:

- *Initial N:* 1,200 literature citations
- *Attrition:* 21 randomized trials were included in the analysis with 3,821 subjects (83% female)
- *Age:* Four to 17.3 years
- *Ethnicity:* Not stated
- *Other relevant demographics:* Not applicable
- *Anthropometrics:* None stated
- *Location:* Study locations were stated as:
    - Switzerland
    - Australia
    - Gambia
    - China
    - Beirut

- New Zealand
- Hong Kong
- US
- United Kingdom
- Israel
- Finland.

Summary of Results:

- The literature search yielded over 1,200 citations. Of these, 29 were eligible for inclusion, but eight were further excluded for a variety of reasons described
- The remaining 21 studies enrolled 3,821 subjects (83% female subjects=12 studies)
- Duration of most studies was 12-18 months.
- The studies were stratified into three categories:
  - Those employing vitamin D supplementations alone
  - Those using calcium or milk plus vitamin D
  - Those with calcium/milk supplementation alone.
- Initially, all randomized trials employing a calcium/milk supplement alone experimental arm were pooled using total body (TB) BMC as the outcome of interest, yielded a non-statistically significant increase in BMC of 2g (supplemented vs. controls).
- A statistical test for homogeneity gave a value of Q equal to 20.46. With 11 degrees of freedom, the hypothesis that the pooled data are homogeneous was rejected since the P-value associated with a Q of 20.46 is less than 0.04 and suggesting substantial heterogeneity across the studies and indicating that the calculated summary mean difference in BMC (2.05) was not valid
- Sensitivity analyses suggested that baseline calcium intake could potentially account for the statistical heterogeneity. The data indicate that calcium supplementation for 18-24 hours at the levels used in relevant studies increases total body BMC by almost 50g (on average) specifically when subjects with calcium/daily nutrient intakes were below recommended levels. This result is 25 times larger than that seen among children with normal dietary intake of calcium/daily nutrients
- Given the few number of studies they could not determine the effect of calcium on lumbar spine BMC
- Overall, there was a suggestive potential association between calcium intake and whole body BMC, but the data were too sparse to draw a firm conclusion.

Author Conclusion:

The authors conclude that increased intake of dairy and calcium-containing products, with and without vitamin D, significantly increases total body and lumbar spine bone mineral content in children with low-baseline intakes.

Reviewer Comments:

Research Design and Implementation Criteria Checklist: Review Articles

Relevance Questions

1.	Will the answer if true, have a direct bearing on the health of patients?	Yes
2.	Is the outcome or topic something that patients/clients/population groups would care about?	Yes
3.	Is the problem addressed in the review one that is relevant to nutrition or dietetics practice?	Yes
4.	Will the information, if true, require a change in practice?	???

Validity Questions

1.	Was the question for the review clearly focused and appropriate?	Yes
2.	Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search termsused described?	Yes
3.	Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	Yes
4.	Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	Yes
5.	Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	Yes
6.	Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Yes
7.	Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?	Yes
8.	Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes
9.	Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes
10.	Was bias due to the review's funding or sponsorship unlikely?	Yes